Science and the Regulation of Biological Products

From a Rich History to a Challenging Future

Food and Drug Administration
Center for Biologics Evaluation and Research

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Message from the Center Director

July 1, 2002 marks the passage of the 1902 Biologics Control Act, which gave the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) the authority to regulate biological products and ensure their safety for the American public. This year, CBER commemorates passage of the Act and 100 years of biologics regulation with a series of events, including a scientific symposium and an exhibit at the Smithsonian National Museum of American History.

Since passage of the Act, CBER has established a proud record of regulatory stewardship and research accomplishments. CBER's tradition of integrating strong science with innovative regulation has enhanced its ability to protect the public health and has led to safer and more effective biological products.

This brochure highlights some key research contributions made by CBER scientists over the last 100 years, and offers a glimpse into the exciting and challenging future of biomedical discoveries and regulation.

From a Rich History to a Challenging Future

The United States Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) is commemorating the Biologics Control Act of 1902 and 100 years of regulating biological products. This law was enacted by Congress to ensure the protection of Americans by providing consistently safe biological products. The Act not only serves as the underpinning for today's regulation of biological products, but also marks a historic turning point in the way America protects the health of its citizens.

Throughout the 20th century, the world witnessed great discoveries in the biological sciences, many of which led to the prevention or eradication of diseases that have devastated populations in the past. For 100 years, what is now known as FDA's Center for Biologics Evaluation and Research or "CBER," has played a significant role in ensuring the safety and efficacy of the fruits of these scientific discoveries. CBER is responsible for the regulation of "biologics," which are medical products such as vaccines, blood and blood derivatives, allergenic patch tests and extracts, HIV and hepatitis tests, gene therapy products, cells and tissues for transplantation, and new treatments for cancers, arthritis, and other serious diseases. CBER reviewed the first vaccines to immunize persons against infectious diseases, such as polio, pertussis ("whooping cough"), and German measles. CBER research led to important discoveries to safely collect, prepare, and transfuse blood and blood plasma.

With continued advancements in medical research and medical technology, CBER will face new challenges – not just scientific and regulatory, but legal and ethical. In the 21st Century, CBER will continue its rich tradition of melding strong scientific research with innovative regulations that ensure timely access to safe and effective biological products.

The St. Louis Tragedy and Enactment of the 1902 Biologics Control Act

In 1901, diphtheria patients were routinely treated with antitoxin derived from the blood serum of horses. The horse serum was manufactured in local establishments with no central or uniform controls. In St. Louis, Missouri, the blood of a tetanus-infected retired milk wagon horse named Jim was used for that purpose. By late 1901, this situation erupted into tragedy when 13 children who had been given diphtheria antitoxin died of tetanus.

In 1902, Congress enacted the Biologics Control Act, also known as the Virus-Toxin Law, which gave the government its first control over the processes used for the production of biological products. The first regulations under this Act became effective on August 21, 1903, and mandated that producers of vaccines be licensed annually for the manufacture and sale of vaccines, serum, and antitoxins. Manufacturing facilities also were required to undergo inspections, and licenses could be revoked or suspended when necessary. Production was to be supervised by a qualified scientist. All product labels were required to include the product name, expiration date, and address and license number of the manufacturer. These new controls marked the beginning of a basic change in America's federal public health policy and a steadfast commitment to the protection of public health.

Additional legislation was passed that eventually would provide further protections for recipients of biological products. In 1906 the Federal Food and Drugs Act was passed, which outlawed adulterated and misbranded foods and drugs, but made no reference to biologic products. This Act was later replaced by the 1938 Food, Drug and Cosmetics Act. After 1938, the appropriate provisions of the 1902 and 1938 Acts were used to regulate biologics.

Polio Vaccine

Vaccine research flourished as new techniques for growing viruses in tissue culture were discovered. An intense focus of vaccine-related research was polio. This highly contagious disease paralyzed or killed its victims, and children were especially vulnerable. Americans were frightened of this disease and were eager to have a vaccine. Ruth Kirschstein, MD, Acting Director, the National Institutes of Health (NIH), remembers: "When I was 10 years old in 1936, there was a big epidemic of polio in the country and I remember my parents and I lived in an apartment house right across the street from the park. And they would take me to the park everyday in the summer and sit me down and say, 'don't talk to anybody, don't go near anybody, don't do anything because you might get polio.' That was the thing people were most scared about and having their children end up in iron lungs. We've gotten rid of all that, and it's just absolutely marvelous."

Jonas Salk's killed polio virus vaccine had to be tested in human trials before licensing. Injections were given to 1.8 million children, making it the largest clinical test of a drug or vaccine in medical history. The Salk polio vaccine was determined to be safe and effective. Later, however, in a tragic set of circumstances known as the "Cutter Incident," more than 260 people contracted polio from a vaccine produced by Cutter Labs. Two batches of the Cutter vaccine were found to contain live polio virus. On May 7th, 1955, the US Surgeon General recommended that all polio vaccinations be suspended until a thorough inspection of each manufacturing facility and review of the procedures for testing vaccine safety had been completed.

In the late 1950's, Albert Sabin theorized that the weakened, live-virus polio vaccine would provide longer lasting immunity. His vaccine was tested in field trials in the Soviet Union between 1957 and 1959, and was licensed in the US by 1962. The Sabin vaccine was endorsed by the American Medical Association and became the primary weapon for polio prevention in the United States by the end of the 1960s. Even though some cases of polio still occurred from this vaccine, it was primarily used because it was inexpensive and easily administered. Now, however, with polio on the brink of eradication throughout the world, the Salk inactivated vaccine is the only product recommended for routine childhood vaccination in the United States.

German Measles Vaccine

In 1964, a global epidemic of rubella, also known as German measles, spread to the United States. An estimated 12.5 million cases of rubella were reported in this country, and 20,000 infants were born with birth defects as a result of the epidemic. Since unborn fetuses were especially vulnerable to the virus, it was imperative that an effective vaccine be developed. In 1966, former CBER directors Paul D. Parkman, MD, and Harry M. Meyer, Jr., MD, then working as scientists in the NIH's Division of Biologics Standards (CBER's predecessor agency), reported that they had developed the first effective experimental vaccine for rubella. "I think the early challenge was to try and develop a credible research program dealing with German measles or rubella. The virus was just isolated, so you didn't know a lot about it. You didn't have good laboratory tests, so we worked on developing a simple, reliable test, so you could tell whether the person had German measles or not from testing their blood," notes Dr. Parkman. Drs. Meyer and Parkman prepared a weakened, live vaccine for human testing and inoculated 34 children. None of the children developed rubella nor did they transmit the disease to their unvaccinated playmates. Dr. Parkman continues, "The experimental vaccine we made was shown not to be communicable. In the middle of all of this the US had the biggest rubella epidemic ever, and there were maybe 20,000 babies with birth defects across the country that resulted from rubella in that epidemic." By 1988, only 225 cases of rubella were reported in the United States.

Pertussis Vaccine

Whooping cough or pertussis vaccine had been available since 1915 but results from its use were not entirely satisfactory. There were many concerns regarding the potency of the vaccine. Several tests were conducted during the 1940s on the potency and effectiveness of this vaccine in mice. In 1944, Dr. Margaret Pittman in the Biologics Control Laboratory (now CBER) developed a potency assay for a pertussis vaccine. By 1949, manufacturers were able to sell whooping cough vaccine approved on potency as well as on safety and sterility. As noted by Dr. Pittman in *A Life with Biological Products*, "I pointed out that some bacteria had a capsule, others secreted an exotoxin. What was the specific antigen of B. pertussis?

It suddenly dawned on me that it was an exotoxin. I was chagrined. Of course, there was a thread of evidence running through the literature. It was not until my fourth presentation of this hypothesis that its significance was recognized."

The vaccine in use today was licensed by CBER on July 31, 1996. It is the first acellular pertussis vaccine for use in infants and children two months of age and older for the primary series of immunizations. This new vaccine contains only the parts of the pertussis bacterium thought to be important for immunity, so it protects infants against whooping cough, while causing fewer side effects than the whole-cell pertussis vaccines that were on the market previously.

Blood and Plasma Products

The 1950s, 60s and 70s were dynamic years for biologics regulation. Evidence at the time indicated that blood obtained from commercial blood banks carried a greater risk of hepatitis transmission. This led to more careful testing, and to increased regulation of blood to further protect the blood supply. According to John Finlayson, PhD, Associate Director for Science in CBER's Office of Blood Research and Review, "Hepatitis loomed very large. Most of us talked about serum hepatitis and that it was a very large threat post-transfusion. We had no tests for hepatitis A, no tests for hepatitis B, and of course, hepatitis C had not even been discovered, so that was a very big challenge, and there was also the challenge that there could be post-transfusion bacterial infections."

During World War II, there were two major concerns – providing clean blood and preserving blood plasma. However, when soldiers were transfused, they had no guarantee of receiving clean blood because none of the tests used today, such as assays to detect hepatitis B or hepatitis C infection, was available. Furthermore, because plasma was pooled for preservation, one infected donor could contaminate an entire batch. In response, Edwin Joseph Cohn, an American chemist, led a team that devised a method called fractionation that separated the individual proteins out of plasma. The resulting protein products, known as plasma derivatives, could be given in response to specific medical needs and with a high degree of confidence that they were safe.

AIDS and the Blood Supply

Additional safeguards implemented over the years for blood donor screening, and blood collection, processing, and testing led to increased confidence and perhaps a relative degree of complacency in the United States concerning the safety of the blood supply. Thus, the scientific and health care community, as well as government agencies and the public, were not prepared when AIDS – acquired immunodeficiency syndrome – emerged with full fury in the1980s. In an era of preventative medicine and cures, there was no way to reverse the lethal virus. Since the human immune deficiency virus (HIV) had been found in the blood of infected people, the appearance of AIDS in the United States threatened the safety of the US blood supply. Transfusions became suspect. Improved screening tests for donated blood were necessary to protect the American people. CBER researchers and the blood and medical products industries responded to the challenge. The first test kit to detect HIV in donated blood was licensed in 1985. Inspections of blood banks were increased to ensure compliance with strict screening and processing procedures. Today, highly sensitive and specific nucleic acid-based tests that decrease the "window" period of detection can be used to screen blood donors for hepatitis and HIV, thus further ensuring the safety of blood, blood components, and blood derivatives.

Challenges for the 21st Century

The discovery of DNA opened the door to a new science – human gene therapy. With the publication of Watson and Crick's pioneering work in 1953 came new hope for sufferers of genetic diseases. The structure that they proposed, the double helix, is the DNA molecule in a human cell that contains genetic information. Understanding DNA allows researchers to manipulate genes and potentially cure inherited diseases. The discovery of recombinant DNA methods led the way to the development of biotechnology. An early outgrowth of biotechnology was the first recombinant DNA vaccine, Hepatitis B (Recombinant), licensed in 1986. Says Philip Noguchi, MD, Director, Division of Cellular and Gene Therapies for CBER, "Gene therapy is either very complicated or very simple. It is a means by which you can actually alter the genetic makeup of a cell. Instead of giving a person interferon – which is a protein used to treat certain cancers and other diseases – why not give the person the gene and then his own body will actually start to make the protein, and might never have to replace it again? That's one of the very intriguing theories of gene therapy."

New therapies such as xenotransplantation (the transplantation of animal cells, tissues or organs into a human) offer hope for an added source of organs. Dr. Noguchi asks, "One of the challenges in using animal tissues or organs is how do you test for what's infectious? Our biggest challenge over the next century or maybe even less than a century is going to really be to understand this, and how can we make sure that when we repair, replace, restore, regenerate, that it's done in a safe manner?"

New vaccines are being developed and modified as new discoveries teach us more about the human immune system. New allergenic products provide relief for Americans who suffer from allergies. Infectious diseases, both new and old, create an urgent demand for the hastened availability of new drugs.

And the genomics and proteomics revolution has scarcely begun. The study of gene structures is leading to potentially effective treatments for a variety of serious diseases and conditions including cancer, diabetes and heart disease. Yet while the genome represents the information archive of the cell, it is the proteins that do all the work. They carry out cellular functions, underpin disease processes, and ultimately dictate cellular growth and death. The main analytical tool being used to study gene structure and proteins is microarray equipment, which is capable of analyzing thousands of genes simultaneously. The joint CBER / NIH Proteomics Program offers molecular imaging of cells and blood, providing early diagnosis of disease and early warning of drug toxicity.

CBER's major challenge for the 21st Century is to expedite approval of biological products for use by the public while, at the same time, maintain high levels of safety and quality. CBER's careful risk management of approved products already in the market also plays an important and essential role in protecting the public health.

Says CBER Director Kathryn C. Zoon, PhD, "This is a moment in time where we are witnessing the exciting and significant progress made in the field of biotechnology. New biological products such as vaccines and therapeutics have already improved the health of the public. The blood supply has never been safer. And, as we move through the 21st century, our strong leadership in science-based regulation, coordinated research, and the use of partnerships will continue to assure that safe and effective new biological products reach the public."

In memory of

Harry M. Meyer, Jr., MD,

Director, Bureau of Biologics,

Food and Drug Administration,

1972-1987.

Dr. Meyer and

Paul D. Parkman, MD

developed the first licensed

rubella virus vaccine.

Commemorating 100 Years of Biologics Regulation

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